# Multi-scale Problem for a Model of Viral Evolution with Random Mutations

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**Abstract** The model of viral dynamics with random mutations is considered. This model describes the cells' population dynamics with significantly different life cycles. The presence of different timescales leads to a singularly perturbed system. The latter makes it possible to apply the technique of separating timescales and thereby reducing the dimensionality of the model.

## 1 Introduction

It is well known that for the singularly perturbed systems with several small parameters Tikhonov's theorem is applicable [3]. In this theorem, the passage to the limit of the solution to a degenerate problem in a system with several small parameters multiplying derivatives is justified. In [1], a similar theorem is formulated and proved for the system of singularly perturbed partial integrodifferential equations with one small parameter. This theorem can be generalized to the case of several small parameters.

Let us consider the singularly perturbed system of integrodifferential equations with two small parameters

$$\begin{aligned} \varepsilon x'_t &= f(x, \int_\Omega g(s, v)ds), \\ \varepsilon \nu v'_t &= h(y, v), \\ y'_t &= w(s, x, y, v, \int_\Omega q(s, r, y, v)dr), \end{aligned} \tag{1}$$

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with the initial conditions $x(0) = x^0,\ v(0,s) = v^0(s),\ y(0,s) = y^0(s)$, where $x$, $v$, $y \in R$, $\varepsilon \ll 1$, $\nu \ll 1$ are the small positive parameters. We assume that system (1) satisfies the following conditions:

(i) The functions $f(x, z_1)$, $g(s, v)$, $h(y, v)$, $w(s, x, y, v, z_2)$, and $q(s, r, y, v)$ and their partial derivatives with respect to all variables are uniformly continuous and bounded in the respective domains $D_1 = \{|x| \le a,\ |z_1| \le b_1\}$, $D_2 = \{s \in \Omega,\ \ |v| \le c\}$, $D_3 = \{|y| \le d,\ |v| \le c\}$, $D_4 = \{s \in \Omega,\ |x| \le a,\ |y| \le d,\ |v| \le c,\ |z_2| \le b_2\}$, and $D_5 = \{s, r \in \Omega,\ \ |y| \le d,\ |v| \le c\}$.

(ii) The equation $h(y, v) = 0$ has an isolated root $v = \varphi(y)$ in the domain $\{|y| \le d\}$ and in this domain the function $v = \varphi(y)$ is continuously differentiable.

(iii) The inequality $h_v(y, \varphi(y)) \le -\alpha < 0$ holds for $|y| \le d$. This condition implies, that the stationary point $\hat{v} = \varphi(y)$ of the first-order associated equation $\hat{v}'_\tau = h(y, \hat{v})$, which contains $y$ as a parameter, is Lyapunov asymptotically stable as $\tau \to +\infty$ uniformly with respect to $y$, $|y| \le d$.

(iv) There exist a solution $\hat{v} = \hat{v}(\tau, s)$ of the initial value problem $\hat{v}'_\tau = h(y^0(s), \hat{v})$, $\hat{v}(0, s) = z^0(s)$ for $\tau \ge 0$, $\forall s \in \Omega$. Furthermore, this solution tends to the stationary point $\varphi(y^0(s))$ as $\tau \to +\infty\ \forall s \in \Omega$, i.e., $v^0(s)$ belongs to the domain of attraction of the stable stationary point $\varphi(y^0(s))$.

(v) The equation $f(x, z_1) = 0$ has an isolated root $x = \psi(z_1)$ in domain $|x| \le a$ and in this domain function $x = \psi(z_1)$ is continuously differentiable.

(vi) The inequality $f_x(\psi(z_1), z_1) \le -\beta < 0\,(z_1 = \int_\Omega g(s, \varphi(y))ds)$ holds for $|y| \le d$, i.e., the stationary point $\hat{x} = \psi(z_1)$ of the second-order associated equation $\hat{x}'_\tau = f(\hat{x}, \int_\Omega g(s, \varphi(y))ds)$, which contains $y$ as a parameter, is Lyapunov asymptotically stable as $\tau \to +\infty$ uniformly with respect to $y$, $|y| \le d$.

(vii) There exists a solution $\hat{x}(\tau)$ to the problem $\hat{x}'_\tau = f(\hat{x}, \int_\Omega g(s, \varphi(y^0(s)))ds)$, with initial value $\hat{x}(0) = x^0$ for $\tau \ge 0$. Further, this solution tends to the stationary point $\psi(\int_\Omega g(s, \varphi(y^0(s)))ds)$ as $\tau \to +\infty$, i.e., $x^0$ belongs to the domain of attraction of the stable stationary point.

(viii) The truncated system

$$\begin{aligned} y'_t &= w(s, \psi(z_1), y, \varphi(y), \int_\Omega q(s, r, y, \varphi(y))dr), \\ x &= \psi(z_1), \\ v &= \varphi(y), \\ z_1 &= \int_\Omega g(s, \varphi(y))ds \end{aligned} \tag{2}$$

with initial condition $y(0, s) = y^0(s)$ has a unique solution $\bar{y}(t, s)$, $\bar{x}(t) = \psi(\int_\Omega g(s, \varphi(\bar{y}(t, s)))ds)$, $\bar{v}(t, s) = \varphi(\bar{y}(t, s))$.

**Theorem 1** *If conditions (i)–(viii) are satisfied, then, for sufficiently small $\varepsilon$ and $\nu$, for some $T > 0$, the problem (1) has a unique solution $x(t, \varepsilon, \nu)$, $v(t, s, \varepsilon, \nu)$, $y(t, s, \varepsilon, \nu)$, which is related to the solution $\bar{x}(t)$, $\bar{v}(t, s)$, $\bar{y}(t, s)$ of the truncated problem (2) by the limit formulas*

$$\lim_{\varepsilon\to+0,\nu\to+0} x(t, \varepsilon, \nu) = \bar{x}(t) = \psi(\int_\Omega g(s, \varphi(\bar{y}(t, s)))ds),\ 0 < t \le T,$$
$$\lim_{\varepsilon\to+0,\nu\to+0} v(t, s, \varepsilon, \nu) = \bar{v}(t, s) = \varphi(\bar{y}(t, s)),\ 0 < t \le T,\ s \in \Omega,$$
$$\lim_{\varepsilon\to+0,\nu\to+0} y(t, s, \varepsilon, \nu) = \bar{y}(t, s),\ 0 \le t \le T,\ s \in \Omega.$$

Note that the limiting equalities for the variables $x$ and $v$ are not uniform for $t \ge 0$. The boundary layer phenomenon occurs [4].

## 2 Model

Let us consider the next model of viral dynamics with random mutations.

$$x'_t = b - \sigma x(t) - \int_\Omega \alpha(s)x(t)v(t, s)ds,$$
$$y'_t = \int_\Omega p_1(s, r)\alpha(r)x(t)v(t, r)\,dr - m(s)y(t, s),$$
$$v'_t = k(s)y(t, s) - c(s)v(t, s).$$

In this model, $x(t)$ is the concentration of uninfected (susceptible) cells at the time $t$, $y(t, s)$, $v(t, s)$ are the density distributions of infected target cells (CD4+ cells, or $T$ helper cells, or Th cells) and free virus particles, respectively, in a one-dimensional phenotype space $s \in \Omega$ at the time $t$. The uninfected cells susceptible to the virus are produced at a constant rate $b$ and die of natural reasons unrelated to the virus infection at a rate $\sigma x(t)$, $\sigma > 0$. The factors $\alpha$, $m$, $k$ and $c$ are characteristics of the virus phenotype, and hence, they are functions of the variable $s$ or $r$. It is assumed that mutations occur in the process of cell infection. Function $p_1(s, r)$ describes the probability that the infected by virus of phenotype $r$ cell produces exclusively virus of phenotype $s$.

It should be noted that there are three very different timescales: life cycles of uninfected and infected cells and free virus particles. The presence of considerably different timescales indicates that the model can be significantly simplified. Following, for example [2], let us introduce the dimensionless variables and parameters

$$t = T\bar{t},\ s = S\bar{s},\ x(t) = X\bar{x}(\bar{t}),\ y(t,s) = Y(\bar{s})\bar{y}(\bar{t},\bar{s}),\ v(t,s) = V(\bar{s})\bar{v}(\bar{t},\bar{s}), \tag{3}$$

$$T = 1/(\mu m_0),\ S = 1,\ X = b/\sigma,\ V = (k_0/c_0)Y,\ Y = b/m_0, \tag{4}$$

where $m_0$, $k_0$, $c_0$ are $m(s)$, $k(s)$, $c(s)$ of the wild (initial or any fixed) strain. $T$ is measured in the units of time, while $X$, $Y$, and $V$ are in the units of concentrations of target cells and free virus.

Substituting (3), (4) into the model and denoting $R_0(\bar{s}) = b\alpha(s)k(s)/(\sigma m(s)c(s))$ (the basic reproduction ratio), $\bar{m}(\bar{s}) = m(s)/m_0$, $\varepsilon = \mu m_0/\sigma$ è $\nu = \sigma/c_0$, we get singularly perturbed ("slow-fast") system with two small parameters:

$$\begin{aligned}
\varepsilon\bar{x}'_{\bar{t}} &= 1 - \bar{x}(\bar{t}) - \int_\Omega R_0(\bar{s})\bar{x}(\bar{t})\bar{v}(\bar{t},\bar{s})\,d\bar{s},\\
\bar{y}'_{\bar{t}} &= \bar{m}(\bar{s})/\mu\left(\int_\Omega p_1(\bar{s},\bar{r})R_0(\bar{r})\bar{x}(\bar{t})\bar{v}(\bar{t},\bar{r})\,d\bar{r} - \bar{y}(\bar{t},\bar{s})\right),\\
\varepsilon\nu\bar{v}'_{\bar{t}} &= c(\bar{s})/c_0\left(\bar{y}(\bar{t},\bar{s}) - \bar{v}(\bar{t},\bar{s})\right).
\end{aligned}$$

Setting $\nu = 0$, we obtain the first-order degenerate system

$$\begin{aligned}
\varepsilon\bar{x}'_{\bar{t}} &= 1 - \bar{x}(\bar{t}) - \int_\Omega R_0(\bar{s})\bar{x}(\bar{t})\bar{v}(\bar{t},\bar{s})\,d\bar{s},\\
\bar{y}'_{\bar{t}} &= \bar{m}(\bar{s})/\mu\left(\int_\Omega p_1(\bar{s},\bar{r})R_0(\bar{r})\bar{x}(\bar{t})\bar{v}(\bar{t},\bar{r})\,d\bar{r} - \bar{y}(\bar{t},\bar{s})\right),\\
0 &= c(\bar{s})/c_0\left(\bar{y}(\bar{t},\bar{s}) - \bar{v}(\bar{t},\bar{s})\right).
\end{aligned}$$

The third equation is algebraic and has root $\bar{v} = \bar{y}$. For the first-order associated equation $\hat{v}'_\tau = c(\bar{s})/c_0\left(\hat{v}(\tau,\bar{s}) - \bar{y}\right)$, where $\bar{y}$ enters as a parameter, the root $\hat{v} = \varphi(\bar{y}) = \bar{y}$ is the asymptotically stable (in the sense of Lyapunov) stationary point. Let us add the initial conditions $\bar{x}(0) = x^0$, $\bar{y}(0,\bar{s}) = y^0(\bar{s})$ and $\bar{v}(0,\bar{s}) = v^0(\bar{s})$. At the initial value of the parameter $\bar{y}$, i.e., at $\bar{y} = y^0(\bar{s})$, the first-order associated equation with the initial condition $\bar{v}(0,\bar{s}) = v^0(\bar{s})$ has a unique solution $\hat{v} = y^0(\bar{s}) + \left(v^0(\bar{s}) - y^0(\bar{s})\right)\exp(-c(\bar{s})/c_0\tau)$, and $\hat{v}(\tau,\bar{s}) \to \varphi(y^0(\bar{s})) = y^0(\bar{s})$ as $\tau \to +\infty\ \forall\bar{s} \in \Omega$. Thereby the initial point $v^0(\bar{s})$ of the first-order associated equation belongs to the domain of attraction of the stable stationary point $\varphi(y^0(\bar{s}))$.

Then let us $\varepsilon = 0$. We obtain the second-order degenerate system

$$\begin{aligned}
0 &= 1 - \bar{x}(\bar{t}) - \int_\Omega R_0(\bar{s})\bar{x}(\bar{t})\bar{v}(\bar{t},\bar{s})\,d\bar{s},\\
\bar{y}'_{\bar{t}} &= \bar{m}(\bar{s})/\mu\left(\int_\Omega p_1(\bar{s},\bar{r})R_0(\bar{r})\bar{x}(\bar{t})\bar{v}(\bar{t},\bar{r})\,d\bar{r} - \bar{y}(\bar{t},\bar{s})\right),\\
0 &= c(\bar{s})/c_0\left(\bar{y}(\bar{t},\bar{s}) - \bar{v}(\bar{t},\bar{s})\right).
\end{aligned}$$

first equation in which is algebraic with respect to $\bar{x}$ and has a root $\bar{x} = \Psi(\bar{v}) = \big(1 + \int_\Omega R_0(\bar{s})\bar{v}(\bar{t}, \bar{s})\, d\bar{s}\big)^{-1}$. This root is the asymptotically stable stationary point (in the sense of Lyapunov) of second-order associated to the equation

$$\hat{x}'_\tau = -\big(1 + \int_\Omega R_0(\bar{s})\bar{v}(\bar{t}, \bar{s})\, d\bar{s}\big)\hat{x}(\tau) + 1.$$

The latter equation with the initial condition $\bar{x}(0) = x^0$ at the initial value of the parameter $\bar{v}$ $\bar{v} = v^0(\bar{s})$ has a unique solution $\hat{x}(\tau) = \big(x^0 - 1/f\big)\exp(-f\tau) + 1/f$, where $1/f = \Psi(v^0(\bar{s})) = 1 + \int_\Omega R_0(\bar{s})v^0(\bar{s})\, d\bar{s}$, for all $\tau \geq 0$, and $\hat{x}(\tau) \to \Psi(v^0(\bar{s}))$ as $\tau \to +\infty$. Thus, the initial point $x^0$ of the second-order associated equation belongs to the domain of attraction of the stable stationary point. Thus, all the conditions of the theorem are satisfied and, consequently, the limiting equalities hold (under the assumption of the existence and uniqueness of the solution of truncated problem).

Thus, the original system can be reduced to a single integrodifferential equation

$$\bar{y}'_{\bar{t}} = \bar{m}(\bar{s})/\mu \left( \int_\Omega p_1(\bar{s}, \bar{r})R_0(\bar{r})\bar{y}(\bar{t}, \bar{r})\, d\bar{r} \Big/ \left(1 + \int_\Omega R_0(\bar{r})\bar{y}(\bar{t}, \bar{r})\, d\bar{r}\right) - \bar{y}(\bar{t}, \bar{s}) \right).$$

## 3 Conclusion

In this paper, we considered the model of viral dynamics with random mutations that contain the population dynamics of uninfected cells, infected cells, and free virus particles. Using the analog of Tikhonov's theorem, timescale separation procedure is carried out. As a result, the original systems of three integrodifferential equations are reduced to a single one. This fact can be used to simplify the numerical simulation of such complex systems. As a rule in evolutionary biology, mathematical models are usually formulated as integrodifferential equations and the same technique can be employed to the ones as well.

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